REMARKS

Claims 81-94, 96-108 and 110-112 are pending. Claims 111 and 112 have been amended. Support for the claim amendments can be found throughout the application as originally filed. No new matter has been added.

Rejection of Claims 111 and 112 Under 35 U.S.C. §112, second paragraph

Claims 111 and 112 are rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner asserts that the claims "are indefinite because [they] ... depend from a canceled claim."

Claims 111 and 112 have been amended to depend from currently pending claims, thereby obviating this rejection.

Rejection of Claims 81-89, 91-94, 96, 97, 99-101, 103, 105-108 and 110 Under 35 U.S.C. §103(a)

Claims 81-89, 91-94, 96, 97, 99-101, 103, 105-108 and 110 are rejected under 35 U.S.C. §103(a), "as being unpatentable over Seed *et al.* (U.S. Patent 6,114,148)." According to the Examiner,

> Although Seed *et al.* do not specifically disclose a synthetic nucleic acid having a continuous stretch of at least 150 common codons or of 60% of the codons of a synthetic nucleic acid sequence, or at least 98% of more of the sequence encoding the protein (e.g., factor VIII or factor IX) are common codons, and the protein is at least 90 amino acid residues in length, at the time the invention was made, it would have been obvious to one of ordinary skill I the art that the reference suggests the nucleic acid sequence has the continuous stretch of common codons cited in the claims because the reference indicates at least 90% of the non-preferred codons in the natural gene are replaced with preferred codons, which includes all or most of non-preferred codons replaced. Thus, the teaching of the reference results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Applicants respectfully traverse this rejection. The present claims are directed to a synthetic nucleic acid sequence which encodes factor VIII or factor IX where at least one non-common codon or less-common codon has been replaced by a common codon encoding the same amino acid residue as the non-common or less-common codon, and the synthetic nucleic acid sequence either: (a) includes at least 98% common codons (claims 89-94, 96, 103-108 and 110); (b) includes a continuous stretch of at least 150 common codons (claims 81-84 and 97-99); or (c) includes a continuous stretch of common codons which includes at least 60% or more of the total codons (claims 85-88 and 100-102). Claims 111-112 cover vectors and cells that include the aforementioned synthetic nucleic acids.

In contrast, Seed et al. provide only a generalized description of optimized nucleic acid sequences that neither teach nor suggest synthetic sequences with the specific range of common codons as presently claimed. In fact, for factor VIII and factor IX, Seed et al. emphasize only partial replacement with preferred codons. The Examiner relies on the following passage in Seed et al. as disclosing the claimed invention: Seed et al. disclose that "at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% of the non-preferred codons in the natural gene are replaced with preferred codons." This passage says nothing about a desirable percentage of preferred codons in the synthetic gene. In fact, the range is so broad as to basically indicate that almost any percentage of the codons can be replaced with preferred codons. In contrast, the present claims require that at least 98% of the codons of the synthetic sequence (or a continuous stretch including at least 150 codons or 60% of the total codons), must be common codons. Further, with regard to the claims that require that all the codons in a synthetic sequence be common codons (e.g., claims 84, 88, 93, 96, 107 and 110), Seed et al. is at best, silent and at worst, dissuasive. As Seed et al. explain, "It is not necessary to replace all less preferred or non-preferred codons with preferred codons. Increased expression can be accomplished even with a partial replacement." (See Seed et al., column 2, line 66 through column 3, line 3). With regard to the factor VIII and factor IX sequences, Seed et al. assert:

> A large fraction of the codons in the human genes encoding Factor VIII and Factor IX are non-preferred codons or less-preferred codons. ***Replacement of a portion of these codons*** with preferred codons should yield genes capable of

higher level expression in mammalian cell culture. (See Seed et al., column 3, lines 34-40, ***emphasis added***).

Thus, by focusing on partial replacement of non-preferred and less-preferred codons, Seed et al. provide neither the teaching nor the motivation for one skilled in the art to arrive at a synthetic sequence, much less a Factor VIII or Factor IX sequence, in which all the codons are common codons.

Moreover, with regard to the claims that recite a synthetic optimized Factor VIII nucleic acid sequence (claims 81-94 and 96), the disclosure of Seed et al. is even more deficient. In fact, Seed et al. directly teach away from the present invention, especially with regard to Factor VIII. In particular, at column 3, lines 25-27, Seed et al. state the following: "In constructing the synthetic genes of the invention it may be desirable to avoid CpG sequences as these sequences may cause gene silencing." In marked contrast, Applicants' disclosure teaches and claims an optimized synthetic beta domain deleted (BDD) Factor VIII nucleotide sequence in which all codons are common codons and in which "the GC content of the sequence increased from 44% to 64%" compared to the wild-type sequence (see page 43, lines 3-11 of the present application). Further, Applicants found that "systemic codon optimization (***with disregard to CpG content***) provides a fruitful strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes." See page 43, lines 25-28 of the specification (***emphasis added***). Thus, one of ordinary skill in the art would not have been motivated to construct a synthetic Factor VIII nucleic acid as presently claimed because modifying the Factor VIII sequence in such a way would have resulted in up to a 50% increase in the GC content of the nucleic acid sequence. Given the teachings of Seed et al., such a modification, at the time the application was filed, would have been predicted to cause gene silencing. Thus, Seed et al. clearly teach away from the claimed invention, particularly with regard to the claims reciting Factor VIII.

For the reasons discussed above, Applicants respectfully request that the Examiner withdraw this rejection.

Attorney's Docket No.: 10278-009001 / 9924

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 8/6/04

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